REMARKS

Upon entry of the foregoing amendments, claims 1 to 6, 8 to 20, 36, 38, 40, 42, 44, 46, and 48 to 64 will be pending in the present patent application. Claims 8, 9, 15 to 20, 36, 38, 40, 42, 44, 46, and 48 have been amended. Claims 50 to 64 are new. New claims 50 and 51 find support in old claims 8 and 9, respectively. New claims 52 to 57 find support in old claims 15 to 20, respectively. New claims 58 to 64 find support in old claims 36, 38, 40, 42, 44, 46, and 48.

Claims 7, 21 to 35, 37, 39, 41, 43, 45, and 47 have been withdrawn as being directed to non-elected subject matter. Applicants reserve the right to pursue patent protection in a timely filed divisional application directed to the non-elected subject matter.

The Office Action includes rejections under 35 U.S.C. § 112, first paragraph, and 35 U.S.C. § 103(a). In view of the remarks to follow, Applicants request that these rejections be reconsidered and withdrawn.

Discussion of the Rejection Under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 9 to 20, 36, 38, 40, 42, 44, 46, and 48 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Although Applicants have amended the afore-mentioned claims in view of a telephone conference with Examiner Seaman on September 22, 2005, Applicants nonetheless traverse respectfully this rejection as the law with respect to the written description requirement has been misapplied in the present rejection.

The function of the description requirement is to ensure that the inventor had possession of, as of the filing date of the application relied upon, the specific subject matter

later claimed by him; how the specification accomplishes this is not material. *In re Smith,* 178 USPQ 620 (CCPA 1973). The claimed subject matter need not be described *in haec verba* to satisfy the description requirement. *In re Smith,* 173 USPQ 679 (CCPA 1972). A written description requirement issue involves the question of whether ***the subject matter of a claim*** is ***supported by the disclosure*** of an application as filed. MPEP § 2163.01. Thus, the test for sufficiency of support is whether all the limitations that define the claimed invention appear in the specification. *Lockwood v. American Airlines*, 41 USPQ2d 1614, 1618 (Fed. Cir. 1989). The present rejection, however, appears to be applying the test ***backwards***.

In this regard, Applicants' claim 8, for example, defines a "method for the treatment or prophylaxis of cardiovascular diseases, metabolic diseases, cancerous diseases or fibrotic diseases, in a patient in need thereof, comprising administering to the patient a pharmaceutically effective amount of a compound according to claim 1." The Action asserts that the "instant specification does not adequately describe the nexus between the modulation of the NHE-1 receptor and useful treatment of a disease/condition" (Action at 3). Significantly, Applicants' claims do not include express recitations directed to a "nexus" or to "modulation of the NHE-1 receptor," which the Action alleges are unsupported by the specification. Indeed, Applicants are not aware of any requirement to recite a particular mechanism in a "method of treatment" claim.

Applicants' representative, the undersigned, called Examiner Seaman on September 22, 2005 to request clarification of the rejection. Examiner Seaman explained that, although the Office is presently developing guidelines with respect to "method of treatment" claims, the Office nonetheless requires such claims to recite a mechanism.[1] Accordingly, Applicants have amended claims 9 to 20, 36, 38, 40, 42, 44, 46, and 48 to include the recitation "to

[1] If Applicants' representative has mischaracterized information provided by the Examiner during the September 22, 2005 telephone conference, the Examiner is requested respectfully to clarify such information in the next Action.

inhibit the cellular sodium-proton antiporter (Na+/H+-exchanger) activity." Examiner Seaman indicated that such amendment would be acceptable.

Although the Applicants appreciate the Examiner's indication that such amendment is sufficient to overcome the rejection for alleged lack of compliance with the written description requirement of 35 U.S.C. § 112, first paragraph, Applicants submit respectfully that the Office's requirements are contrary to the law with respect to the written description requirement. As detailed above, the test for compliance with the written description requirement is whether all the limitations that define the claimed invention appear in the ***specification***. In other words, the language of the claims is considered first, followed by consideration of the specification to identify the support. The effect of the Office's requirement that Applicants recite a mechanism, however, is the ***backwards*** application of the written description test because Applicants are required to incorporate limitations ***from the specification into the claims*** to satisfy the written description requirement. Thus, the Office is looking to the specification for claim recitations that it alleges are not described by the specification because such limitations are not recited by the present claims. This is illogical. The purpose of the written description requirement is to ensure that the inventor had possession of, as of the filing date of the application relied upon, the specific subject matter later claimed by him. *In re Smith,* 178 USPQ 620 (CCPA 1973). Indeed, by alleging lack of compliance with the written description requirement and then requiring a limitation from the specification to be transported into the claims is an admission that the written description requirement ***is*** satisfied.

In any event, Applicants have amended claims 9 to 20, 36, 38, 40, 42, 44, 46, and 48 to further prosecution of the present patent application. Old claims 8, 9, and 15 to 20, however, have been presented as new claims 50 to 57 for reconsideration by the Office. In addition, old claims 36, 38, 40, 42, 44, 46, and 48 have been presented as new claims 58 to 64 for

reconsideration by the Office. Applicants request respectfully that, should new claims 50 to 64 be rejected for alleged failure to comply with the written description requirement, the Office provide a comprehensive legal and factual basis in support of such rejection, including why the recitation of a mechanism is required in such claims.

Discussion of the Rejection Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 9 to 20, 36, 38, 40, 42, 44, 46, and 48 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled with regard to the broad use of the compounds of claim 1 for the treatment of the recited diseases. Applicants traverse this rejection because one skilled in the art having read the present specification and claims would be able to make and use the present inventions without engaging in undue experimentation.

The first paragraph of § 112 requires that the disclosure of a patent application be such that persons skilled in the art, having read the patent application, would be able to practice the inventions described by the claims. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). There is no legal requirement that this be done in any particular manner. An enabling disclosure can be provided by the use of illustrative examples or simply by broad terminology. *In re Marzocchi*, 169 U.S.P.Q. 367 (C.C.P.A. 1971). The test of enablement is ***not*** simply whether experimentation would have been necessary, but whether such experimentation would have been ***undue***. *See In re Angstadt*, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *See Wands*, 8 U.S.P.Q.2d at 1404. The factors to be considered in determining whether any necessary experimentation is undue include:

i. the breadth of the claims;
ii. the nature of the invention;
iii. the state of the prior art;
iv. the level of one of ordinary skill;

v. the level of predictability in the art;

vi. the amount of direction provided by the inventor;

vii. the existence of working examples; and

viii. the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Id. (*citing Ex parte Forman*, 230 U.S.P.Q. 546, 547 (Bd. Pat. App. & Int. 1986)). Any conclusion of non-enablement must be based on the evidence as a whole. *Id.* Significantly, a patent application need not disclose what is well known in the art. *Id.*

When rejecting a claim under the enablement requirement of § 112, first paragraph, the Patent Office bears the "initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification." *In re Wright*, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). To object to an applicants' disclosure on the grounds that it is not enabling with respect to the scope of a claim sought to be patented, the Action must identify evidence or technical reasoning supporting any doubts regarding applicants' enablement of the claim. *Id.*; and MPEP § 2164.04. Without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling. *In re Wright*, 27 U.S.P.Q.2d at 1513; *In re Marzocchi*, 169 U.S.P.Q. at 369.

Despite the Action's assertion that those skilled in the art would need to engage in undue experimentation to utilize "the compounds of claim 1 for the treatment of any disease" (Action at 8), a review of the scientific literature reveals that there is no reason to believe that those of ordinary skill would have any difficulty in using the compounds of claim 1 to treat, for example, the conditions recited in Applicants' claims or that, if experimentation ***were*** required, such experimentation would not be routine in nature. For the reasons detailed below, Applicants submit respectfully that consideration of the *Wands* factors relied upon by the Action indeed demonstrate that those skilled in the art would be able to treat the claimed

diseases without engaging in undue experimentation.

The Nature of the Invention

According to the Action, the nature of Applicants' invention is a "method of treating a disorder that is modulated by the NHE-1 receptor" (Action at 5). Applicants disagree respectfully that the claimed invention is a method of treating a disorder that is modulated by the NHE-1 receptor only. Although inhibition of the NHE-1 receptor may be preferred, inhibition of each of the NHE receptors with the compounds of claim 1 is within the scope of the present invention. In any event, the Action has not provided any reason as to how or why this factor contributes to the alleged lack of enablement.

The Predictability in the Art

It is asserted in the Action that "the instantly claimed invention is highly unpredictable since one skilled in the art ... is unable to fully predict possible results from the administration of the compound of claim 1 due to the unpredictability of the role of modulation of NHE-1 receptors" (Action at 5). The Action, however, provides no evidence or technical reasoning in support of such statement. Significantly, the Action appears to have overlooked a plethora of literature that shows the predictable relationship between the inhibition of NHE1 and the diseases recited in Applicants' claims. In this regard, Exhibit A (attached hereto) presents a summary of the literature of which Applicants are aware (along with copies of the literature), which provides strong evidence that those of ordinary skill in the art know the link between inhibition of NHE and the conditions recited in Applicants' claims and that such conditions can be treated or prevented by inhibition of NHE. Indeed, the MPEP makes it clear that "[a] patent need not teach, and preferably omits, what is well known in the art." MPEP § 2164.01. Accordingly, the instantly claimed invention is not "highly unpredictable" as the Action asserts.

The Presence or Absence of Working Examples

The Action admits that the compounds of the present invention inhibit NHE-1 (Action at 6). The action, however, finds fault with the working examples because the compounds allegedly have not been tested for their ability to treat any specific disease or condition (id.); however, a patent need not teach, and preferably omits, what is well known in the art. MPEP § 2164.01. As detailed above, Applicants provide herewith a wealth of literature that provides strong evidence that those of ordinary skill in the art know the link between inhibition of NHE and the conditions recited in Applicants' claims and that such conditions can be treated or prevented by inhibition of NHE.

The Action further points to data that allegedly shows vast differences in activities between compounds that are structurally similar (Action at 6). According to the Action, in view of such data, "it is unclear as to how such activities can be linked to the treatment of diseases/conditions without being directly tested for such activity" (id.). In the first instance, Applicants' claims do not require a specific degree of treatment and the Action has not provided any evidence or technical reasoning to demonstrate that the compounds having the lower activities would ***not*** result in ***some degree*** of treatment. Moreover, even if such differences in activities were to require those of ordinary skill in the art to engage in ***some*** experimentation (*arguendo*), the Action has not provided any evidence or technical reasoning to show that such experimentation would be ***undo***. Thus, in view of the literature submitted herewith, the Action has failed to demonstrate that Applicants' working examples are insufficient to enable the claimed invention.

The Amount of Direction or Guidance Present

The present specification provides ample disclosure to enable the claimed invention. The Action, however, asserts that "there are no examples of the instantly claimed compounds ... actively treating a disease/ condition" (Action at 7). Applicants, however, are not aware

that such examples are required to enable the claimed invention. There is no legal requirement that enablement is accomplished in any particular manner and that an enabling disclosure can be provided by the use of illustrative examples or simply by broad terminology. *In re Marzocchi*, 169 U.S.P.Q. 367 (C.C.P.A. 1971). As detailed above, Applicants submit herewith a wealth of literature that provides strong evidence that those of ordinary skill in the art know the link between inhibition of NHE and the conditions recited in Applicants' claims and that such conditions can be treated or prevented by inhibition of NHE. Accordingly, Applicants' disclosure that the claimed compounds inhibit NHE activity provides ample guidance to those skilled in the art in view of the well-documented link between such activity and the claimed conditions.

The Breadth of the Claims

Applicants submit that, for the reasons detailed above, the full breadth of the claims is enabled by Applicants' disclosure when considered in view of the knowledge in the art.

The Quantity of Experimentation Needed

The Action alleges that the quantity of experimentation needed is undue, in part, because one skilled in the art would need to determine what diseases out of all known diseases would be benefited by the mediation of NHE-1 receptors. This statement, however, is demonstrably false. As detailed above, Applicants have provided a wealth of literature that demonstrates that those of ordinary skill in the art know what diseases/ conditions would be benefited by mediation of NHE-1 receptors. Accordingly, to the extent that any experimentation is required to practice the claimed invention (*arguendo*), such experimentation is far less than that alleged by the Action.

The Level of the Skill in the Art

Applicants agree with Action's statement that the level of skill in the art is high (Action at 7). In view of such high level of skill and the knowledge that such high level

entails (as evidenced by the literature submitted herewith), Applicants submit that the present disclosure enables the full scope of the claims.

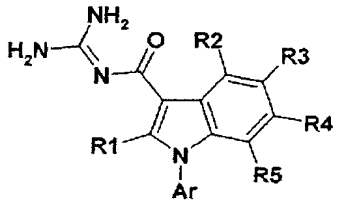
Thus, for all of the reasons detailed above, Applicants' claims are fully enabled by the present disclosure; one skilled in the art would not have to engage in undue experimentation to practice any of the claimed methods. Accordingly, reconsideration and withdrawal of the rejection are requested respectfully.

Discussion of the Rejection Under 35 U.S.C. § 103(a)

Claims 1 to 6, 8 to 20, 36, 38, 40, 42, 44, 46, 48, and 49 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over EP 0 708 091 to Kitano et al. ("the Kitano Reference"). Applicants respectfully traverse this rejection, as the Action has failed to identify any motivation, other than the hindsight provided by Applicants' disclosure, as to why one of ordinary skill in the art at the time of the present invention would have modified the Kitano reference to obtain Applicants' claimed invention.

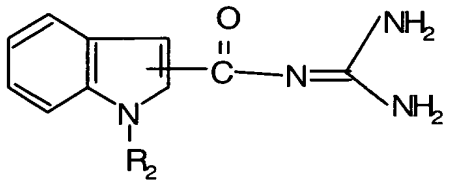
"A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." *In re Kotzab*, 55 U.S.P.Q.2d 1313, 1316 (Fed. Cir. 2000). "The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time." *In re Dembiczak,* 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999) (quoting *Interconnect Planning Corp. v. Feil*, 227 U.S.P.Q. 543, 547 (Fed. Cir. 1985). To establish a *prima facie* case of obviousness, "the examiner must show reasons that the skilled artisan, confronted with the same problem as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." *In re Rouffet*, 47 U.S.P.Q.2d 1453, 1458 (Fed. Cir. 1998).

Applicants' claims define compounds of the formula (I)



(I)

wherein, in relevant part, Ar is a ***9- or a 10-membered bicyclic heteroaryl having one, two or three nitrogen atoms***, which may be linked via any of its positions (*see, e.g.*, claim 1). The Kitano reference, in contrast, defines compounds of the formula



, wherein, to the extent that R_2 is a "heteroaromatic," R_2 is "a 5- or 6-membered aromatic group containing 1 to 4 nitrogen atoms or a 5- or 6-membered aromatic ring containing 1 to 2 nitrogen atoms and one oxygen atom or one sulfur atom" (see the Kitano reference at page 7, lines 21 to 23). Thus, at least one difference between the claimed invention and the Kitano reference is that the size of the group attached to the nitrogen atom in the indol ring. In this regard, the Kitano reference teaches a ***5- or 6-membered heteroaromatic ring*** whereas Applicants' claims require a ***9- or a 10-membered bicyclic heteroaryl*** as defined above.

Although the Action asserts that "it would have been obvious to one of ordinary skill in the art to make compounds [of the Kitano reference] with the equivalent to the Ar being heterocyclic bicyclic ring" (Action at 9), the Action does not identify any reason ***why*** the skilled artisan would have been motivated to so modify the Kitano reference in any way that would have produced a claimed invention. In an apparent attempt to allege motivation for such modification, the Action asserts that the Kitano reference's teaching of a heteroaromatic ring exemplified by pyridine and piperidine would make obvious Applicants' claimed invention. This, however, falls far short of providing the requisite motivation because it has

not been shown ***why*** one of ordinary skill in the art would modify the Kitano reference by replacing its 5- or 6-membered single heteroaromatic ring structure (*i.e.*, pyridine and piperidine) with a ***9- or a 10-membered bicyclic heteroaryl*** as defined by Applicants' claimed invention.

Moreover, the Action's reliance on the Kitano reference's alleged teaching of a heteroaromatic ring exemplified by pyridine and piperidine is misplaced. In this regard, the Action asserts that the Kitano reference "has examples of the [R2] moiety being pyridine and piperidine" (Action at 9). Applicants, however, cannot find such examples in the Kitano reference (and particular cites have not been provided by the Action). To the extent that pyridine and piperidine are disclosed by the Kitano reference such disclosure is in the context of a definition of "aromatic group" at page 7. Thus, because there are no specific examples of compounds wherein pyridine or piperidine are attached to the nitrogen atom in the indole ring, one of ordinary skill in the art would have even less reason to look to such compounds in the disclosure of the Kitano reference. Accordingly, the pyridine and piperidine substituents could not provide the motivation to modify the Kitano reference as is alleged in the Action.

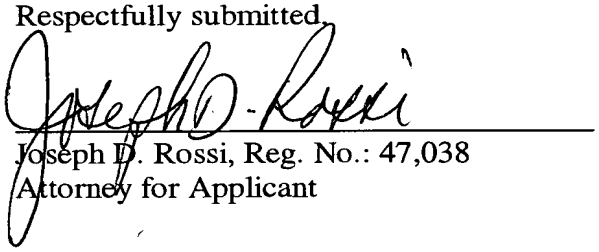
Indeed, the Patent Office has the burden of presenting ***factual evidence*** that would indicate that the claimed methods are *prima facie* obvious. ***In re Lunsford***, 148 U.S.P.Q. 721 (C.C.P.A. 1966). In the absence of such a showing, such a rejection is based upon impermissible hindsight. ***In re Fritch***, 23 U.S.P.Q.2d 1780, 1784 (Fed. Cir. 1992) ("it is impermissible for an Examiner, in proffering a 35 U.S.C. § 103 rejection, to use the claimed invention as an instruction manual or "template" to piece together the teachings of the prior art to render the claimed invention obvious."). Accordingly, reconsideration and withdrawal of the rejection over the Kitano reference are requested respectfully.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the Action of record. Applicants respectfully submit that this application is now in condition for allowance. Accordingly, an indication of allowability and an early Notice of Allowance are requested respectfully.

The Commissioner is hereby authorized to charge the fee required and any additional fees that may be needed to Deposit Account No. **18-1982** in the name of Aventis Pharmaceuticals Inc.

Respectfully submitted,



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